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(54) Title: ORAL PHARMACEUTICAL COMPOSITIONS CONTAINING MELATONIN

(57) Abstract

Oral pharmaceutical compositions containing melatonin as the active principle in form of micro-emulsions are described.

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ORAL PHARMACEUTICAL COMPOSITIONS CONTAINING MELATONIN

The present invention refers to oral pharmaceutical compositions containing melatonin.

Melatonin is an hormone synthesized in the epiphysis, in the retina and, presumably in the chromaffinic cells of the intestinal tract. Its biosynthesis is subjected to a typical circadian rhythm, reaching a peak during the night. Its effects are numerous and particular attention has been recently focused on the immunostimulant and immunomodulatory effect of melatonin. A problem which considerably limits the therapeutic potentials of this hormone is however provided by its poor oral bioavailability.

It has now been found that melatonin may be effectively administered by the oral route when formulated in form of micro-emulsions.

Micro-emulsions are well-known and may be prepared according to conventional methods: a review of their properties and preparative methods has been recently published on Chemistry in Britain Vol. 26 (4) April 1990, 342-344 and cited references.

As a pharmaceutically acceptable emulsifier, lecithins or purified components thereof such as L-α-phosphatidylcholine, L-α-phosphatidylethanolamine or L-α-phosphatidylserine, both extractive and synthetic, are preferred. L-α-phosphatidylcholine is preferably used in a weight ratio to melatonin of about 1:1 in a solution consisting of ethanol, propylene glycol and water.

The active principle and a thickening agent such

as gelatine, natural gums, cellulose derivatives and the like are then added to the above solution obtained by usual methods.

The following example further illustrate the invention.

EXAMPLE

Formulations in micro-emulsions

1.2 g of L-α-phosphatidylcholine are dispersed under vigorous agitations in 4.8 ml of a solution consisting of [ethanol(2)/ propylene glycol (1)]/H_2O = 55/45 pp.

After emulsifying, 1.5 g of melatonin are added, under stirring and then, after complete dissolution, 1 g of gelatine.

The so obtained micro-emulsion, hereinafter referred to as MR-111, has been subjected to pharmacokinetics studies, evaluating the serum levels of melatonin in healthy volunteers, according to the following method.

Experimental part

Two healthy volunteers were treated at the zero (0) time with a dose of 2.5 mg, respectively of melatonin (subject 1) and of MR-111 (subject 2).

5 ml of venous blood were sampled at the times, expressed in minutes, 0, 30, 90, 150, 210, 270 and 330.

After separation, serum was frozen till the melatonin extraction. The extraction and the determination of melatonin were carried out according to the methods of Maestroni et al., J. Neuroimmunol. 13, 19-30, 1986.

Results

Serum levels of melatonin expressed in pg/ml.

Time (minutes)	Melatonin	MR-111
0	25	27
30	362	268
90	1788	719
150	240	984
210	680	844
270	66	439
330	0	295
390	0	199
405	0	93

The administration of 2.5 mg of melatonin (subject 1) confirms the kinetics observed in other studies (Wright J. et al., Clin. Endocrinol., 24, 375-382 (1989); Lieberman H.R. J. Neural. Trans., 21, 233-241 (Suppl.) (1986) with an high peak after 90 minutes and a fast decrease of the plasma concentration.

The product MR-111 induces a wider peak, more similar to the physiological peak of melatonin, surprisingly showing an higher bioavailability.

CLAIMS

1. Oral pharmaceutical compositions containing melatonin as the active principle in form of micro-emulsions.

2. Compositions according to claim 1, characterized in that the micro-emulsion is obtained by using L-α-phosphatidylcholine as emulsifier and a mixture consisting of ethanol, propylene glycol and water as solvent.

3. Compositions according to claim 1 or 2, also containing thickening agents.

4. Compositions according to claim 3, wherein the thickening agent is gelatine.

5. Compositions according to any one of the previous claims, wherein the weight ratio of L-α-phosphatidylcholine to melatonin is about 1:1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01486

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/107 A 61 K 31/40

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	FR,A,2255897 (DI BELLA) 25 July 1975, see the whole document, in particular page 5, line 9 - page 6, line 5	1-5
A	EP,A,0211258 (ABBOTT LABORATORIES) 25 February 1987, see abstract; pages 16-18; examples 1,2	1-5
A	FR,A,2618351 (MERO ROUSSELOT SATIA) 27 January 1989, see the whole document	3,4

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08-11-1991	11. 12. 91
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Dagmar Frank

Mme Dagmar FRANK

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9101486 SA 50061

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2255897	25-07-75	AU-A- 7194974	05-02-76
		BE-A- 824022	16-04-75
		CH-A- 625218	15-09-81
		DE-A- 2435365	29-01-76
		GB-A- 1493941	30-11-77
		JP-A- 50096565	31-07-75
		NL-A- 7417046	02-07-75
EP-A- 0211258	25-02-87	AU-B- 589430	12-10-89
		AU-A- 6021486	05-02-87
		JP-A- 62029511	07-02-87
FR-A- 2618351	27-01-89	None	

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82